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Review

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T lymphocytes linking autoimmunity and cardiovascular disease in aging

Enrique Ortega-Sollero[1], Ignacio Ruíz-Fernández[1], Pilar Martín[1,2]

[1]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Cardiovascular Risk Factors and Brain Health Program, Madrid 28029 Spain.
[2]CIBER de Enfermedades Cardiovasculares (CIBER-CV), Madrid 28029, Spain.

Correspondence to: Dr. Pilar Martín, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Cardiovascular Risk Factors and Brain Health Program, Melchor Fernández Almagro 3, CIBER-CV, Madrid 28029, Spain. E-mail: pmartinf@cnic.es

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Abstract

Aging alters the immune system, leading to immunosenescence characterized by impaired T cell functions. The balance between regulatory T cells and type 17 helper T (Th17) cells is crucial for maintaining peripheral immune homeostasis. Aging disrupts this balance, contributing to a systemic chronic proinflammatory environment that increases the prevalence of age-related diseases. The Treg/Th17 imbalance compromises self-tolerance, promoting autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Furthermore, chronic inflammation driven by aberrant T cell responses is a significant risk factor for the progression of cardiovascular diseases (CVD), including hypertension, atherosclerosis, myocardial infarction, and myocarditis. Autoimmune disorders further exacerbate the risk of CVD, which remains the leading cause of mortality among patients with autoimmune diseases. This review provides an in-depth analysis of the mechanisms driving Treg/Th17 imbalance during aging, highlighting its impact on immune homeostasis, autoimmunity, and cardiovascular health. It explores how inflammaging and T cell dysfunction contribute to diseases such as rheumatoid arthritis, systemic lupus erythematosus, atherosclerosis, and myocardial infarction, emphasizing shared pathways and therapeutic strategies to restore immune balance and mitigate chronic inflammation. Understanding these immune pathways highlights the therapeutic potential of restoring Treg/Th17 balance to restore immune tolerance and reduce chronic inflammation, thereby mitigating the onset and progression of these age-related conditions.

Keywords: T lymphocytes, cardiovascular disease, aging, autoimmunity, Th17, Tregs

INTRODUCTION

T lymphocytes play a key role in the adaptive immune system[1]. Among these cells, the balance between regulatory T (Treg) cells and type 17 helper T (Th17) cells is crucial to maintaining peripheral immune homeostasis[2,3]. However, with age, this balance may become impaired, leading to an increased risk of autoimmune diseases and cardiovascular conditions[4,5].

During aging, the immune system undergoes significant alterations, leading to a process known as immunosenescence, which disrupts various immune functions, including those of T cells[6]. This contributes to a systemic chronic proinflammatory environment, leading to increased susceptibility to infections and a higher prevalence of age-related diseases (ARDs)[7-9]. Such changes in immune balance can lead to self-tolerance breakdown, promoting autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis[10,11]. Furthermore, chronic inflammation driven by the overactivation of T cell responses has also been defined as a key factor in the progression of cardiovascular diseases (CVD) such as atherosclerosis, myocardial infarction, and heart failure[7,12,13]. Additionally, autoimmune events are reported to increase the risk of CVD[14] and the synergic severity of both is a topic of growing concern because CVD is one of the major causes of mortality in patients with autoimmune conditions[15].

In this review, we explore the common mechanisms that render aging individuals more susceptible to autoimmune diseases and CVD. We focus on the pivotal role of T lymphocyte biology, particularly the Treg/Th17 balance, which is crucial for maintaining immune homeostasis and self-tolerance [Figure 1]. Aging disrupts this equilibrium, resulting in a chronic inflammatory state known as inflammaging, which promotes autoimmune pathologies, such as rheumatoid arthritis and systemic lupus erythematosus, and increases the risk of CVD, including atherosclerosis and myocardial infarction. We examine how immunosenescence contributes to the dysregulation of T cell subsets and the molecular drivers of their pathogenic activation. By identifying these shared pathways, we highlight the potential of targeting Treg/Th17 imbalance as a therapeutic strategy to mitigate the inflammatory and immune dysfunctions that exacerbate age-related diseases. This comprehensive overview aims to bridge the gaps in our understanding of T cell-mediated mechanisms underlying the dual burden of autoimmunity and CVD in aging populations.

T LYMPHOCYTES

Th17 biology and their implications in autoimmunity

Th17 lymphocytes are a subset of $CD4^+$ cells characterized by the production of interleukin-17 (IL-17)[16]. The differentiation of these lymphocytes is driven by a combination of cytokines and transcriptions factors: after binding of a major histocompatibility complex (MHC) class II-bound peptide and an appropriate secondary signal, exposure to IL-6 and transforming growth factor-beta (TGF-β) promotes the expression of the retinoic acid receptor-related orphan receptor gamma-t (RORγt), the main transcription factor of Th17 cells[16,17]. Exposure to IL-23 is required for stabilization and is essential for the proinflammatory activity of this subset of lymphocytes[17].

The main cytokines produced by Th17 cells are IL-17A, IL-17F, IL-21, and IL-22. IL-17A and IL-17F are key for neutrophil recruitment and activation, promoting inflammation and antimicrobial responses[18]. IL-22 is involved in multiple aspects of epithelial barrier function, such as regulating epithelial cell growth and permeability, generating mucus and antimicrobial proteins (AMPs), and producing complement[19]. Therefore, Th17 lymphocytes play a pivotal role in epithelial barrier sites such as the skin, lungs, oral cavity, gastrointestinal tract, and vagina[20].

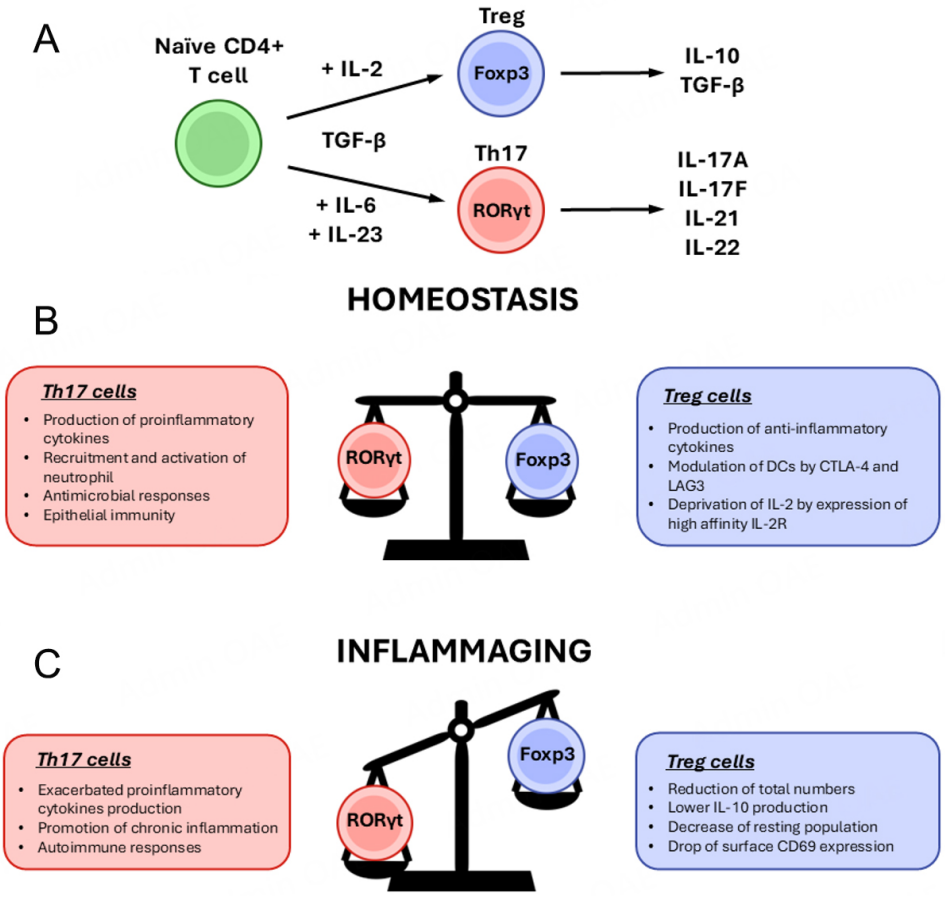

Figure 1. (A) Treg and Th17 lymphocyte differentiation. Treg and Th17 lymphocytes share a common signaling pathway by TGF-β. The cytokine milieu plays a key part in the differentiation to these different subsets. Upon exposition to IL-6 or IL-23, naïve $CD4^+$ lymphocytes differentiate into Th17 cells. The main cytokines produced by Th17 cells are IL-17A, IL-17F, IL-21, and IL-22. On the other hand, in the absence of proinflammatory cytokines, TGF-β alone or together with IL-2 drives the differentiation to Tregs. Tregs produce anti-inflammatory cytokines such as IL-10 and TGF-β. (B) In homeostasis, there is a balance between Treg and Th17 populations. The main function of Th17 cells is host defense against extracellular pathogens, whereas Tregs' main functions are to maintain peripheral immune tolerance and modulate immune responses. (C) During inflammaging, the Treg/Th17 balance is disrupted. Exacerbated Th17 responses lead to autoimmunity and inflammatory diseases and Tregs are described to be less tolerogenic. TGF-β: Transforming growth factor-beta; RORγt: retinoic acid receptor-related orphan receptor gamma-t; Foxp3: forkhead box p3; DCs: dendritic cells; CTLA-4: cytotoxic T lymphocyte antigen 4; LAG-3: lymphocyte-activation gene 3.

Although the main function of these cells is host defense against extracellular pathogens[2], exacerbated Th17 responses can lead to autoimmunity and inflammatory diseases[21]. IL-17-mediated recruitment of immune cells promotes chronic inflammation and, eventually, autoimmune disorders[22]. Inhibiting Th17 differentiation or blocking IL-17A/IL-23 with monoclonal antibodies has proven to be an effective therapeutic approach to mitigate these phenomena[23,24].

Treg and their roles in autoimmunity

Treg lymphocytes are a subpopulation of $CD4^+$ cells specialized in maintaining peripheral immune tolerance and modulating immune responses to prevent autoimmunity[1]. They are essentially characterized by the expression of the transcription factor Foxp3[25].

Depending on the conditions under which Tregs develop, different types of this subset have been described[26]. Thymus-derived Tregs, known as tTregs, are generated during T cell maturation in the thymus and play an important role in avoiding organ-specific autoimmunity[27]. Extrathymically generated Tregs, known as pTregs, are formed at peripheral sites under tolerogenic conditions such as exposure to antigens with TGF-β and IL-2[27,28]. These types of Tregs are prevalent in certain organs, such as the maternal placenta and the gut. Therefore, their main function is to maintain tolerance toward the fetus during pregnancy, as well as to foods and commensal bacteria[29]. Single-cell RNA sequencing has revealed heterogeneity within Treg populations, indicating specialized functions in different tissues[30].

To perform their immunomodulatory functions, Tregs employ several mechanisms[31]. On the one hand, Tregs modulate dendritic cell function and maturation through the expression of cytotoxic T lymphocyte antigen 4 (CTLA-4) and lymphocyte-activation gene 3 (LAG3), as well as by binding to CD80/86 costimulatory molecules and MHC class II, subsequently leading to the production of indoleamine 1,3-dioxygenase (IDO) and the inhibition of effector T cell (Teff) activation[32,33]. Studies have shown that mice lacking both LAG3 and programmed cell death protein 1 (PD1) experience spontaneous myocarditis with extensive infiltration of activated T cells and macrophages. Based on these findings, the authors concluded that deleting LAG3 and PD1 disrupts peripheral tolerance by Tregs, which promotes antigen-specific effector phenotype marked by increased IFNγ and IL-17 production in $CD4^+$ and $CD8^+$ cells[34,35].

Additionally, Tregs can cause metabolic disruption by expressing CD39, an ectoenzyme that generates adenosine, thereby inhibiting Teff cell responses[36]. Another mechanism employed by Tregs is the deprivation of IL-2 from Teff cells through the expression of a high-affinity IL-2 receptor, effectively starving these cells of survival signals[37]. Lastly, Tregs produce anti-inflammatory cytokines such as IL-10 and TGF-β, which suppress Th17 and type 1 helper T (Th1) proinflammatory responses[38].

Recent studies have evaluated the role of Tregs in autoimmune diseases such as type 1 diabetes, multiple sclerosis (MS), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA)[39]. In humans, CD25 deficiency has been described to cause immunodeficiency without altering Treg numbers but with reduced IL-10 production[40,41]. Tregs have proven to be a promising therapeutic target for treating these diseases. However, the complexity and heterogeneity of autoimmune conditions present significant challenges. Treg-based therapies are being explored to restore immune tolerance, ranging from non-cell-based approaches, such as low-dose IL-2, to cell-based therapies, including autoantigen-specific T cell receptor (TCR) Tregs[42].

Treg/Th17 balance

Treg and Th17 lymphocytes share a common differentiation pathway mediated by TGF-β. The cytokine milieu plays a crucial role in the differentiation to these subsets. As previously mentioned, when naïve $CD4^+$ lymphocytes are exposed to IL-6 or IL-23, they differentiate into Th17 cells. IL-6 and TGF- β drive Th17 differentiation through the phosphorylation and activation of the signal transducer and activator of transcription 3 (STAT3)[43]. STAT3 inhibits Treg differentiation by downregulating Foxp3[44].

Conversely, in the absence of proinflammatory cytokines, TGF-β alone or in combination with IL-2 drives differentiation into Tregs[10,16]. IL-2 signaling in Tregs leads to the phosphorylation of the signal transducer and activator of transcription 5 (STAT5), promoting Foxp3 expression and inhibiting the STAT3 signaling pathway[40]. Another molecule described as having an immunomodulatory role in controlling Treg/Th17 balance is CD69. This protein is a C-type lectin disulfide-linked homodimer expressed on all hematopoietic cells except erythrocytes[45]. Upon interaction with its ligands, JAK3 is recruited to the cytosolic tail of CD69, phosphorylating STAT5, which promotes Treg differentiation and function while inhibiting Th17

differentiation[46,47] [Figure 2].

Therefore, IL-6 and IL-21 promote Th17 differentiation and suppress the expression of genes associated with Treg cells. Once infection or inflammation is resolved, IL-6/IL-21 levels decline, allowing TGF-β to restore Tregs and suppress Th17, thus regaining immune homeostasis and preventing tissue damage from chronic inflammation[48]. Altogether, maintaining the fitness of this balance is crucial to maintain homeostasis.

INFLAMMAGING

Aging is a complex phenomenon that encompasses different genetic, epigenetic, mitochondrial, and cellular processes acquired gradually over time, disrupting homeostasis and leading to morbidity and a limited lifespan. The hallmarks of aging, which define its characteristics, are often shared with chronic diseases or ARDs, including oxidative stress, genomic and epigenetic instability, cellular senescence, and impaired intercellular communication[49,50]. Among ARDs, the most common can be categorized into the following groups: tumors, neurological pathologies, metabolic disorders, autoimmune responses, and cardiovascular conditions[51].

One of the recently recognized hallmarks of aging and a susceptibility factor for ARDs is a chronic, low-grade, systemic inflammatory signature known as inflammaging[50]. This condition arises from the accumulation of molecular and cellular changes in the immune cells, which adopt an immunosenescent state that can also affect other cell lineages. It is primarily characterized by increased unresponsiveness, ineffective immune responses, and an inflammatory cytokine signature[52]. Other senescent cell populations contribute to this state by inducing a senescence-associated secretory phenotype (SASP), which amplifies inflammaging in a positive-feedback loop, resulting in elevated levels of circulating and tissue cytokines such as IL-6, IL-8, or IL-1β[53].

The aging T cells

All immune cells contribute to inflammaging and are, in turn, affected by it. However, in recent years, growing evidence has shown that T cells undergo significant alterations and play a central role in this process. Due to their nature, T cells are not abundant in tissue infiltration, but their activation state and communication with other immune and non-immune cells can disrupt homeostatic balance. This disruption can trigger the development of ARDs when T cells become senescent and their presence in tissues increases[8,9].

On a systemic level, thymic involution and cumulative genomic and mitochondrial alterations gradually skew the T cell pool toward a less naïve and more memory-effector T cell phenotype. One of the contributing factors to this phenomenon is the higher incidence of age-related clonal hematopoiesis, which also reduces the TCR repertoire[54]. While the long-term presence of effector memory T cells is beneficial for swift responses to re-encounters with pathogens, their accumulation over time creates a T cell pool with limited capacity to recognize new antigens, reduced plasticity, and senescent and exhausted features. These characteristics trigger the release of inflammatory cytokines, further contributing to inflammaging[6,55,56].

While the Th1/Th2 balance and $CD8^+$ T cell compartments have traditionally been considered key players in orchestrating inflammaging[7], the contribution of the Th17 pool has gained prominence, particularly in the context of age-related autoimmunity. In the cytokine milieu of aging animals, $CD4^+$ naïve cells have been shown to differentiate into a Th17 phenotype more readily and exhibit a stronger cytokine signature compared to younger individuals[57,58]. This leads to an increased and more active pool of cells expressing IL-17, contributing to the risk of developing ARDs.

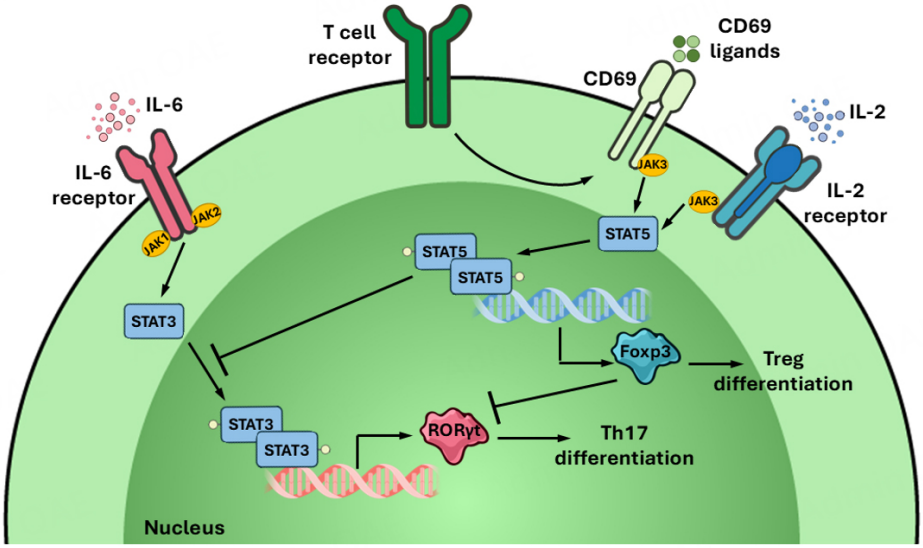

Figure 2. Signaling pathways of Treg and Th17 lymphocyte differentiation. Upon interaction with IL-6, the cytoplasmic tail of IL-6R associates with Jak1 and Jak2, triggering phosphorylation of Stat3 and its translocation to the nucleus, where it can activate the transcription factor RORγt and induce Th17 cell differentiation. On the other hand, Treg differentiation is triggered by IL-2R and CD69 in a non-redundant way. After interaction with IL-2 or CD69 ligands (OxLDL, alarmins S100A8/A9 or Gal-1), Jak3 is recruited in the cytoplasmatic tails of IL-2R and CD69, respectively. Then, STAT5 is phosphorylated, dimerized, and translocated to the nucleus, where it promotes the expression of Foxp3. IL2R/CD69-dependent activation of STAT5 inhibits the Th17 cell differentiation pathway by preventing SSTAT3 translocation to the nucleus and suppressing STAT3-mediated RORγt activation through the induction of Foxp3 expression. STAT: Signal transducer and activator of transcription; Jak: Janus Kinase; RORγt: retinoic acid receptor-related orphan receptor gamma-t; OxLDL: oxidized low-density lipoprotein; Foxp3: forkhead box p3.

Regarding the Treg compartment, the literature presents conflicting evidence about this subset in aging. Some studies report a decrease in this population[3], while others indicate an increase or no significant change in total numbers[56,59]. When examining the immunomodulatory activity of Treg cells, a similarly inconsistent pattern emerges. However, there is some consensus that aged Tregs exhibit a diminished ability to downregulate the expression of IL-17 and IL-2 by T cells, while showing little or no difference in their effect on the release of IFNγ[59-62]. These findings suggest that the presence and functionality of this subset are highly species- and context-dependent, warranting further research to better understand the topic.

Along with these intrinsic factors, the accumulating exposure to toxins and bad habits has a direct effect on immune aging. First, dietary patterns such as caloric restriction have been shown to mitigate T cell immunosenescence by reducing markers of T cell exhaustion and enhancing the function of naïve and memory T cells[63]. Common dietary habits in the current society have also been linked to disruption of the Treg/Th17 balance: a high-salt diet is known to enhance Th17 responses in the gut, leading to systemic IL-17 signatures[64] and a western, high-fat diet induces the rupture of this balance, which promotes metabolic imbalance[65].

Pollution further exacerbates T cell aging by introducing toxins that disrupt homeostasis. Apart from inducing common hallmarks of aging such as shortened telomeres and mitochondrial dysfunction[66], the immune system is affected by changing the architecture of pulmonary lymph nodes and impairing macrophage activity, which indirectly affects T cell-mediated immunity[67].

Another poor lifestyle habit is cigarette smoking, which significantly impacts T cells by altering their function and balance. Generally, smoking increases proinflammatory Th1 and Th17 cells, contributing to

diseases like chronic obstructive pulmonary disease (COPD), Crohn's disease, and psoriasis, while also promoting Th2-mediated allergic inflammation, such as asthma. Smoking effects on Tregs are mixed, with evidence of both increased and decreased levels, but studies agree on decreasing immunomodulatory functions. Moreover, smoking enhances CD8+ T cell numbers and cytotoxic activity, especially in the lungs[68].

Altogether, these inherent changes and environmental factors affect the Treg/Th17 balance during the lifespan of individuals, contributing to inflammaging and the development of ARDs[3,69].

T CELLS IN AGE-RELATED DISEASES

The role of T lymphocytes in ARDs has become a topic of growing interest in recent years, particularly regarding the imbalance of Treg and Th17 populations during aging. Immunosenescence has been highlighted as a factor negatively affecting other systems, prompting increased efforts by the scientific community to characterize the molecular changes underlying the Treg/Th17 imbalance and its contribution to the chronic disruption of homeostasis. This review aims to elucidate the role of these cells in ARDs, with a special focus on autoimmune and cardiovascular events.

T cells in age-related autoimmunity

Autoimmune disorders arise when an immune response against a self-antigen is established. Self-reactive T cells and the breakdown of tolerance are critical for the development of these conditions. The role of Th17-derived cytokines and the state of the Treg compartment are pivotal in these disorders, most of which are predominantly Th17-driven[7]. Although these disorders can occur at any age and are often linked to genetic predisposition, age and immunosenescence have also been identified as risk factors due to the compromised state of the immune system and T cells, which can lead to a breakdown of tolerance[11].

Thymic involution is one of the triggers that compromise tolerance. Central tolerance is disrupted due to impaired migration of thymocytes into the medulla and reduced expression of tissue-restricted antigens (TRAs) by the shrinking population of medullary thymic epithelial cells (MTECs)[70]. Several pathways lead to this effect, including nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome activation[71], and the epithelial-mesenchymal transition process that MTECs undergo[72,73], among many others. The resulting hindered negative selection leads to an increased release of self-reactive T cells exiting the thymus. Additionally, the generation of tTregs is reduced with age due to competition from pTregs re-entering the thymus[74].

Additionally, the multiple mechanisms of peripheral T cell tolerance, as described by ElTanbouly *et al.*[75], are also altered over time to varying degrees:

• The quiescence state of the T cell pool is essential to prevent T cell hyperactivation. However, this state becomes impaired with age as the immune system shifts from a predominantly naïve population to an increased presence of effector memory T cells[6]. This shift creates a state more prone to the expansion and proliferation of T cell clones. Additional evidence indicates that the absence of checkpoint molecules during the early stages of T cell activation, such as VISTA or RUNX1, promotes an age-related proinflammatory signature and the development of various autoimmune events[76-78].

• T cell ignorance of self-antigens is compromised when physical barriers break down, exposing T cells to previously immunoprivileged organs and tissues. With age, changes in the architecture of these barriers enable increased leakage from blood vessels into tissues and vice versa, allowing previously hidden self-

antigens to be encountered by T cells[79]. One prominent example of this phenomenon is the blood-brain barrier (BBB), which becomes more permeable with age[80]. Additionally, an age-related proinflammatory environment can facilitate T cell infiltration into organs, further increasing the availability of these antigens.

• The mechanisms of anergy and exhaustion both serve to induce a hyporeactive state at the pre- or post-T cell activation stage, respectively, through the high expression of inhibitory receptors. While anergy is not necessarily a feature of the aging immune system, exhausted T cells accumulate in the elderly due to repeated exposure to antigens. However, these cells do not appear to directly contribute to autoimmune events and may even have a protective effect, as their unresponsiveness can benefit the outcome of autoimmune conditions[81]. Their presence, nonetheless, negatively impacts the diversity of the TCR repertoire, making organisms more susceptible to chronic infections. Furthermore, a distinct exhausted-like population of $CD8^+$ T cells has been identified as inducing a SASP in tissues through the release of granzyme K[82]. Although not directly linked to aging, studies suggest that the anergic population of self-reactive T cells can differentiate into Tregs, thereby preventing autoimmunity[83].

• Although senescence in aging T cells shares overlapping features with anergic and exhausted states, these cells exhibit a proinflammatory cytokine signature that significantly impacts the microenvironment and triggers autoimmune events. This occurs not only by inducing the breakdown of tolerance but also by creating a positive feedback loop with other immune and non-immune cell types with a SASP[11,52].

• The deletion or death of the self-reactive T cell population is impaired due to the previously mentioned decrease in tTreg generation and the rendered suppression mechanisms of both tTregs and pTregs[56,59,74]. Additionally, the high levels of TNF-α and IL-6 observed in the elderly can easily skew the Treg/Th17 balance toward a proinflammatory phenotype by interfering with Foxp3 expression[69].

Altogether, these age-related changes result in a damaged immune system that is unable to function as it once did. Further studies are needed to fully comprehend the extent to which each of these factors contributes to the overall state of immune dysfunction. It is evident that these changes collectively predispose individuals to the development of autoimmune diseases and the breakdown of tolerance. Identifying these shared mechanisms may lead to the discovery of new therapeutic targets to battle autoimmune conditions in the elderly.

To study the mechanisms of aging in the immune system, there are scarce mouse models that recapitulate what happens in the clinic. Preclinical models are usually mice aged after reproductive senescence. These animals show reduced naïve T cells, lower CD8/Treg ratios, and increased chronic inflammation, and are used to study cancer immunotherapy responses, age-related immune dysfunction, and Treg dynamics in tumors[84]. The transgenic $Lmna^{G609G}$ progeria mouse serves as an exceptional animal model for investigating Hutchinson-Gilford Progeria Syndrome (HGPS) in humans. In this model, the reported thymic retardation was suspected to be linked to elevated cellular senescence, a hypothesis supported by the marked increase in senescence-associated β-galactosidase-positive cells observed in the thymic tissue of $Lmna^{G609G}$ mice. Additionally, a more pronounced inflammatory response in the skeletal muscle is observed in $Lmna^{G609G/+}$ mice with multifocal lymphocyte infiltration along with occasional plasma cells[85,86]. Another study has described that aryl hydrocarbon receptor (AHR) deletion also results in accelerated aging with an earlier inflammatory signature and, consequently, detrimental cognitive effects[87]. Another model specific for T cell aging is the $Tfam^{fl/fl}$ $Cd4^{Cre}$ mice, which show accelerated age-related features at two months of age[88]. Altogether, these models offer valuable insights into the broader and complex mechanisms underlying physiological aging in humans.

While the mechanisms described above contribute to the development of autoimmune phenomena in general, it is worth mentioning the role of the age-related Treg/Th17 imbalance in the following conditions.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with a higher prevalence in pregnant women (ranging between 17 and 50 years old). In women, the incidence peaks at ages 20-25 years (3.6 per 100,000 person-years) and has a second peak around menopausal age (~65 years)[89]. It is characterized by systemic inflammation and significant damage to multiple organs[90,91]. Extensive research in recent decades has established the pivotal roles of Th1, Th2, and Th17 cytokines in the pathogenesis of SLE, as well as the disruption of their plasma levels in this disease[92]. Although the molecular mechanisms remain unclear, the Treg/Th17 imbalance plays a central role in the pathogenesis of SLE. In fact, elevated levels of IL-17 have been observed in the plasma of SLE patients, correlating with an increased frequency of Th17 cells in their peripheral blood[93]. In a lupus model, the absence of IL-17 resulted in improved nephritis due to the downregulation of IgG, IgG1, and IgG2a production. Additionally, IL-17 blockade ameliorated SLE by suppressing B cell differentiation within germinal centers[94], proving the counter-regulatory role of Th17 cells in SLE. Metabolic abnormalities in T lymphocytes from SLE patients and lupus-susceptible mice have been reported[93]. These defects include mitochondrial dysfunction, such as elevated transmembrane potential, reduced ATP synthesis, and increased ROS production. T cells also exhibit hyperactivated glucose metabolism, with elevated glycolysis, oxidative phosphorylation, and pentose phosphate pathway activity. SLE patients further display increased expression of the inducible cAMP early repressor (ICER) transcription factor, which drives glutaminolysis and Th17 differentiation. Additionally, $CD4^+$ T cells in SLE patients show a highly activated mTOR pathway due to mitochondrial hyperpolarization and overactivation of the pentose phosphate pathway. This promotes Th17 differentiation while impairing Treg differentiation and function, leading to detrimental outcomes[95-97]. Notably, these mitochondrial changes observed in SLE are also hallmarks of aging and immunosenescence[50,52], which may explain the increased prevalence of the disease as the population ages. Additionally, Th2 cells also contribute to SLE pathogenesis by promoting humoral responses, although their impact is less pronounced than Th17 and is often mediated through specialized subsets like Tfh2[92].

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the synovial joints, leading to bone destruction[98]. A key hallmark of RA patients is premature T cell aging due to accelerated immunosenescence. The distinctive features of prematurely aged T lymphocytes include the loss of CD28 expression, a reduction in naïve T cells due to thymic involution, an expanded memory repertoire, telomere shortening, increased cytotoxicity, DNA damage accumulation, impaired cell cycle arrest, increased apoptosis, and massive proinflammatory cytokine secretion[99]. A Treg/Th17 imbalance has also been observed in RA patients, with a decrease in Treg ($CD4^+CD25^{high}CD127^-$) numbers and an increase in Th17 ($CD4^+CCR6^+CXCR3^-$) cells[98]. This imbalance correlates with elevated serum levels of IL-17, IL-21, IFNγ, and IL-2. Building on this imbalance, a recent study identified SMAD3 and STAT3 as potential biomarkers for the diagnosis of this condition[100].

Further, high levels of IL-6, commonly observed in aged individuals, have been found to play a crucial role in promoting the development of Th17 cells over Tregs in the periphery of RA patients. Blocking IL-6 has been shown to ameliorate disease progression[101]. This finding further reinforces the link between inflammaging and the higher prevalence of late-onset cases.

Multiple sclerosis

Multiple sclerosis (MS) is another age-related autoimmune disease characterized by a Treg/Th17 imbalance[102]. The peak of prevalence is highest in the 50-59 age group (378 per 100,000) and declines after 70 years old. Mean age at diagnosis has increased, with a bimodal distribution peaking around 30 and 40-45 years and late-onset cases (more than 50 years old) rose from 2.6% (pre-1970) to 11.9% (post-2010)[103]. Its etiology is not fully understood and can occur at any age, but the increasing prevalence of late-onset cases is often associated with immunosenescence and the leakage of the BBB, both of which are crucial for its development[104]. This leakage exposes self-antigens, triggering tissue-damaging Th17 responses[105,106]. Myelin-reactive $CD4^+$ T cells lead to demyelination of the central nervous system (CNS), resulting in significant neurological disability[107,108]. Elevated numbers of Th17 cells are found infiltrating the cerebrospinal fluid (CSF) and spinal cord, with high expression of very late antigen-4 (VLA-4)[109]. Mechanistically, Th17 cells contribute to MS pathogenesis by producing glutamate upon interaction with oligodendrocytes. Higher levels of this molecule may cause oligodendrocyte damage and expose myelin antigens, thereby activating autoreactive T lymphocytes[110]. Additionally, Th17-derived IL-17 promotes lymphocyte migration by upregulating the expression of CCL2, CXCL8, and IL-6 genes in endothelial cells of the BBB[111,112]. Conversely, Tregs in MS exhibit impaired immunomodulatory function and decreased resting populations[113]. The proinflammatory environment encountered by Tregs at CNS lesion sites may be the primary cause of their weakened anti-inflammatory activity[114].

T cells in age-related CVD

As previously mentioned, CVD is one of the most common groups of ARDs and is strongly associated with immunosenescence, remaining the leading cause of death worldwide, with a higher prevalence among the elderly[7]. Senescent T lymphocytes act as risk factors for CVD by increasing vascular inflammation and arterial blood pressure, particularly in patients with viral infections. For instance, elevated levels of senescent Th17 and $CD4^+$ effector memory cells in patients with HIV infection have been linked to a higher incidence of heart failure and atherosclerosis[115]. Moreover, senescent T cells are directly involved in the pathogenesis of age-related CVDs, including vascular conditions such as hypertension, certain forms of vasculitis and atherosclerosis, as well as cardiac diseases like myocardial infarction and myocarditis. The specific roles of these lymphocytes require further investigation to improve our understanding of these pathologies and to position T cells as potential therapeutic targets for ameliorating the outcomes of age-related CVDs.

Hypertension

Aging increases the prevalence of arterial stiffening and hypertension, with more than two-thirds of patients being older than 65 years of age. Additionally, the inflammaging state has been linked to the development of hypertension[116]. T lymphocytes, in particular, play an active role in regulating blood pressure by performing prohypertensive functions in the kidney, sympathetic outflow from the CNS, and the regulation of interstitial sodium storage in the skin[117]. Hypertensive patients exhibit elevated numbers of senescent T lymphocytes, particularly $CD8^+CD28^-CD57^+$, which produce high levels of IFNγ. Studies have shown that angiotensin II promotes helper T cell differentiation into an effector phenotype, facilitates their mobilization from lymph nodes, and contributes to vascular injury through endothelial and kidney infiltration[118,119].

In mice, a high-salt diet has also been identified as a major contributor to T cell activation in hypertension, including the production of neoantigen, sodium itself and the activation of the sympathetic nervous system[117]. These stimuli drive Th17 differentiation and a systemic IL-17 signature through the glucocorticoid-regulated kinase 1 (SGK1) and IL-23R pathway, ultimately leading to vascular remodeling and dysfunction[120]. In contrast, Tregs modulate angiotensin II-induced hypertension by producing IL-10,

which stabilizes endothelial function and reduces blood pressure[121]. Studies using high-salt diet models of hypertension may also highlight a potential Treg/Th17 imbalance in idiopathic cases in humans.

Giant cell arteritis

Giant cell arteritis (GCA) is a vasculitis affecting large vessels, characterized by granulomatous arterial wall inflammation, with a higher prevalence in patients over 50 years[122]. The Treg/Th17 balance is disrupted in GCA patients. On the one hand, Th17 cells play a role in GCA by inducing acute vessel inflammation through neutrophil and macrophage recruitment. On the other hand, a reduction in both the number and functional capacity of Tregs has been observed in this disease. Studies have revealed Treg plasticity in CGA, where IL-17A$^+$Tregs are associated with a favorable prognosis, indicating some residual immunomodulating capacity of these lymphocytes[123]. Moreover, other studies have shown that CD8$^+$Treg cells exhibit a greater degree of impairment in aged GCA patients compared to age-matched individuals. This impairment is attributed to the downregulation of NADPH oxidase 2 (NOX2) secreted in exosomes by these lymphocytes, which dampens CD4$^+$ T cell proliferation[124,125].

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease that can progress into acute coronary syndrome (ACS). Studies have demonstrated that a Treg/Th17 imbalance in aged patients promotes inflammation, plaque destabilization, and the onset of ACS[5,126,127]. The leukocyte activation antigen CD69 has been described as having an atheroprotective role by maintaining Treg/Th17 balance. It is required to activate the STAT5 pathway in Foxp3$^+$ cells, regulating tTreg cell development and peripheral Treg homeostasis[128]. The binding of an oxidized low-density lipoprotein to CD69 confers a regulatory phenotype to human and mouse T cells, dampening Th17 responses through the activation of NR4A nuclear receptors and ameliorating atherosclerosis[129].

There are contradictory studies indicating whether IL-17 is proatherogenic[130], atheroprotective[131], or has no role in atherosclerosis[126]. Immune cells, including T cells and macrophages infiltrating the adventitia layer in aged arteries, are a significant source of inflammatory cytokines and ROS production. ROS activate nuclear factor κB (NFκB), leading to the activation of proinflammatory genes such as TNF-α and IL-6. Age-associated increases in NFκB activity have been directly implicated in arterial dysfunction in older rodents and patients[13]. Moreover, an accumulation of senescent CD4$^+$CD28^{null} T lymphocytes has been observed in coronary atherosclerotic plaques. These senescent T cells produce granzymes and perforin, which directly damage the endothelium and vascular smooth muscle cells. Furthermore, CD4$^+$CD28^{null} T cells release high levels of IFNγ, inducing macrophage activation and the production of metalloproteinases that degrade the extracellular matrix, promoting plaque formation[132].

Additionally, patients with a higher frequency of CD4$^+$CD28^{null} T cells experience recurrent acute coronary events compared to those with a single event, indicating that atherosclerosis promoted by senescent T cells represents a risk factor for other CVDs[118]. Conversely, Treg activity, though the secretion of IL-10 (which suppresses effector T cells and macrophages) and TGF-β (which stabilizes plaques), has been shown to have atheroprotective effects in mice and aged patients[133]. Overall, Treg/Th17 balance is being investigated as a potential therapeutic target to mitigate atherosclerosis.

Acute myocardial infarction

Acute myocardial infarction (AMI) is primarily caused by a reduction or cessation of blood flow to a portion of the heart, resulting in myocardial necrosis[134]. Advanced age and unhealthy lifestyle choices, such as smoking and poor dietary habits, significantly increase the risk of AMI[135]. This ischemic event triggers an

inflammatory response that leads to the formation of a collagen-rich scar. T lymphocytes and their cytokines play crucial roles in the initiation, progression, and resolution of inflammation following AMI[136]. Particularly, Th17 cells contribute to heart damage by producing IL-6 and IL-21, along with IL-1β and TNF-α secreted by macrophages, which amplify the inflammatory response, causing chemotaxis and activation of neutrophils in the damaged heart[135]. Notably, IL-21 is used as a biomarker for myocardial function after AMI. $Ly6C^{low}$ macrophages facilitate scar formation and prevent expansion of the infarct area during the early stages of AMI. Moreover, these macrophages showed upregulated IL-21R expression compared to $Ly6C^{high}$ macrophages, highlighting the critical role of this cytokine. Furthermore, IL-21-deficient mice showed a shorter inflammatory response post-AMI, along with improved survival and cardiac function compared to WT mice[137]. A recent study characterized an elevated subset of senescent and memory $CD4^+$ $CD57^+$ T cells in the PBMCs of AMI patients after a six-month follow-up. The higher production of IFNγ and TNF-α by this subset was associated with increased short-term cardiovascular mortality and heart failure[138].

Additionally, Tregs have emerged as key players in protecting against cardiac damage after AMI[139]. There is rapid recruitment of Tregs to the injured myocardium, mediated by the CXCL12/CXCR4 axis and galectin-1. A recent study demonstrated that CD69 expression on Treg limits the severity of cardiac damage after AMI by inducing aryl hydrocarbon receptor (AhR)-dependent CD39 ectonucleotidase activity, which reduces IL-17 production and promotes apoptosis of pathogenic γδ T cells[140]. There is a pressing need for studies investigating the age-related Treg/Th17 imbalance during and after AMI. Such research could help identify potential therapeutic targets in this population to improve outcomes following ischemic events in older patients.

Myocarditis

Myocarditis is a disease that can be triggered by various agents, including infectious pathogens, toxins, drugs, and autoimmune disorders. It may resolve spontaneously, result in sudden death or progress to dilated cardiomyopathy (DCM)[141]. Regardless of its etiology, all cases share an inflammatory and autoimmune response driven by cardiac myosin-specific Th17 lymphocytes. This is explained by the lack of representation of myosin heavy chain-α (MyHCa) peptides by MTECs. As a result, cardiac myosin-specific lymphocytes are not eliminated, allowing them to leave the thymus and remain primed for activation in peripheral lymphoid tissues[142]. A recent study involving 795 patients with a mean age of 70 years found that thymic alterations, such as thymoma, increase the incidence and worsen the prognosis of myocarditis, particularly in patients treated with immune checkpoint inhibitors (ICIs)[143]. Regarding ICI treatment, myocarditis is one of the rarest adverse events (0.04%-1.14%) but has the highest mortality rates (50% monotherapy and 60% ICI combination). On the one hand, ICI treatment activates the aforementioned cardiac myosin-specific Th17 lymphocytes. On the other hand, immunotherapy disrupts cardiac homeostasis, leaving the heart vulnerable to autoimmune attack[144].

Myocarditis is a Th17-driven autoimmune disease, characterized by an increased ratio of Th17 cells to both Th1 cells and Tregs, as well as an increased absolute number of Th17 cells in the peripheral blood of mice and human cases[145]. CD69 negatively regulates heart-specific Th17 responses, cardiac inflammation, and heart failure progression during myocarditis[146]. Additionally, senescent Th1 cells play a key role in myocardial aging by generating localized inflammation in the heart, leading to mild functional impairment that may trigger autoimmune events[147]. The role of Th17 and Tregs in myocarditis, as well as CD69 expression in this subset in aged individuals, needs further characterization to identify potential therapeutic targets. The actual prevalence of the disease remains unknown due to the challenges in achieving a definitive diagnosis, as the gold standard, endomyocardial biopsy, is highly invasive[148]. Overall, the Treg/

Th17 imbalance is central to the pathophysiology of myocarditis. Further investigation of this balance during aging is essential to deepen understanding of the disease and to prevent sudden death or chronic heart failure resulting from DCM development after myocarditis.

T cells in age-related CVD in autoimmune disorders

As previously mentioned, the rise of autoimmunity during aging is quite common. Not surprisingly, the presence of a concomitant autoimmune disease is a significant risk factor for developing CVDs other than myocarditis[15]. Abnormal lymphocyte function and elevated levels of proinflammatory cytokines are central to both groups of diseases, contributing to vascular dysfunction, impaired resolution of inflammation, and the promotion of chronic inflammation. Additionally, the loss of tolerance to self-antigens and the generation of autoantibodies, key characteristics of autoimmunity, are also implicated in the aberrant inflammatory response observed in CVDs[149].

The heart is a common target for the side effects of autoimmune diseases. The cardiac damage associated with these conditions is complex and multifaceted, often involving chronic inflammation, immune complex deposition, oxidative stress, and vascular endothelial dysfunction. These processes can result in myocardial fibrosis, early-onset coronary atherosclerosis, and varied clinical manifestations depending on the specific autoimmune disorder.

The underlying mechanisms of cardiac damage in autoimmune diseases need further exploration[150], although some autoimmune conditions have been found to be more frequently linked to cardiac involvement than others. For instance, a novel study by Martini *et al.* discovers an autoimmune-like mechanism underlying pressure overload-induced heart failure (PO-HF)[151]. This work reveals that T cells and antibodies can independently transfer cardiac dysfunction to healthy mice. Through a novel antigen discovery pipeline, the authors identified three cardiac self-antigens (YWHAZ, SNRPD1, and ATP5O) that induce pathogenic immune responses that are recognized by T cells in a subset of human heart failure patients. Most importantly, oral tolerization with these peptides prior to disease induction significantly reduced cardiac dysfunction, inflammation, and stress markers, mostly via the induction of effector Treg cells[151]. These findings strongly support that autoimmunity plays a direct role and is a functional driver of cardiovascular diseases.

Additionally, several autoimmune diseases are associated with a significantly increased risk of atherosclerosis. Patients with autoimmune disorders exhibit a higher prevalence of dyslipidemia compared to the general population[152]. The serum lipid profile in SLE patients shows elevated levels of triglycerides and VLDL, along with lower levels of HDL cholesterol, compared to age-matched controls[153]. Cellular cholesterol metabolism, which modulates T cell function, is disrupted in SLE patients, resulting in reduced numbers and impaired suppressive functions of Tregs[154]. Dyslipidemia may contribute to the loss of peripheral tolerance by Tregs, triggering the production of antibodies against atherosclerosis-associated antigens and promoting an aberrant immune response in atherosclerotic patients with autoimmune disorders[149]. Another hypothesis that may explain the correlation between autoimmunity and atherosclerosis in the elderly is the aging vasculature, a shared feature of both conditions[79,155].

Specific autoimmune conditions have also been linked to the development of age-related CVDs. Due to the systemic nature of SLE, several organs are eventually affected during the course of the disease. However, a higher mortality rate is observed in patients with a concomitant CVD, including premature atherosclerosis, endocarditis, and valve disease. The overactivation of T cells in SLE, particularly Th17, promotes vascular injury and clot formation. Treg dysfunction in this disease leads to a loss of cardiovascular protection.

Hyperactive T cells become less responsive to Treg counter-regulation due to decreased IL-10R expression, resulting in endothelial tissue damage driven by a significant increase in IL-10 in the surrounding medium[156].

RA-associated CVDs include heart failure, ischemic heart disease, pericarditis, myocarditis, cardiomyopathy, cardiac amyloidosis, coronary vasculitis, arrhythmias, and valvular diseases. The presence of local inflammation in the myocardium and epicardium, combined with fibrosis, generates diastolic and systolic dysfunction, leading to cardiac hypertrophy. These changes in myocardial tissue can result in arrhythmias, heart failure, and sudden death[157]. RA can induce atrial fibrillation by increasing the number of cardiac fibroblasts and upregulating TNF-α and IL-6. These proinflammatory cytokines are involved in pathophysiological processes, including atrial fibrosis, atrial myocardial apoptosis, and atrial electrical remodeling[158]. Among RA patients, those with atrial fibrillation show higher Th17 and Th1 numbers in their blood, along with an increased Th17/Treg ratio in peripheral blood[159], highlighting the implications of Treg/Th17 imbalance in the development of CVDs in aged patients with autoimmune diseases.

Altogether, age-associated autoimmunity significantly contributes to the increased risk of CVDs in the elderly. The dysregulation of T cell functions, particularly the Treg/Th17 imbalance, results in chronic inflammation, vascular dysfunction, and loss of self-tolerance, which are central factors in both autoimmune diseases and CVDs. Understanding these shared mechanisms is essential for developing targeted treatments to mitigate cardiovascular events in the aging population with autoimmune diseases.

TARGETING T CELLS IN AGE-RELATED DISEASES

Based on the evidence linking T cells to the development of ARDs, it is clear that exploring the therapeutic potential of T lymphocytes will be highly valuable for treating these diseases. Novel studies are focusing on targeting the mechanisms of T cell aging or directly modulating T cell activity to ameliorate these conditions, rather than solely targeting the affected tissues.

T cell-based immunotherapies are being explored to improve outcomes in ARDs. Emerging therapeutics aim to delay the onset of these diseases by modulating T cell responses. These approaches include a variety of strategies, ranging from resetting the immune system and depleting pathogenic T lymphocytes to promoting Treg immunomodulation. By diminishing global T cell function or numbers, pathological T cell activity can be reduced. Promoting Treg responses through the modulation of T cell metabolism or microbiota-based therapies has also been proposed[9]. These new therapies will be further discussed in this section.

The more straightforward approach would be to slow the aging of T cells. Unlike other mechanisms such as anergy or exhaustion, T cell senescence does not appear to offer any evolutionary advantage during aging, except possibly in contexts like lymphomas or chronic infections, where it may help prevent the spread of pathogens. Therefore, targeting this process directly could be beneficial. Some preclinical studies have shown success in targeting senescent non-immune populations[160,161], but directly targeting T cells may be more effective, as senescence-like features in other cell types can sometimes have beneficial effects[162].

More T cell-specific therapeutic approaches are already being implemented. As previously mentioned, T cells from RA and SLE patients often exhibit a loss of CD28 expression. Anti-CD3 monoclonal antibody therapy has been shown to generate antiarthritic $CD8^+$ Treg cells and expand the relative numbers of $CD4^+$ Treg cells[163]. Additionally, monoclonal antibodies targeting proinflammatory cytokines, such as TNF-α, are widely used in RA. For instance, anti-TNF-α therapy (infliximab) has been found to promote CD28 re-

expression in T cells from the peripheral blood mononuclear cells of RA patients[164].

Tocilizumab is a humanized anti-IL-6 receptor antibody that inhibits Th17 cell differentiation by inactivating the STAT3 signaling pathway. It is currently used to treat RA, ischemic events, myocardial infarction, and acute systemic and chronic inflammatory diseases. In the context of myocardial infarction, tocilizumab has been shown to protect against inflammation and myocardial damage induced by the ischemic event, leading to a clinical trial (NCT 02419937) investigating the short-term application of this therapy after myocardial infarction[165].

An alternative approach involves enhancing the anti-inflammatory aspects of T cells. IL-2-based treatments have been employed in recent years to target Tregs and potentially ILC2. These treatments include: (1) immunocomplexes of recombinant IL-2 and antibodies that selectively interact with specific parts of the IL-2R, (2) IL-2 fusion proteins composed of IL-2 conjugated with a second protein (typically CD25 or IL-33), and (3) direct modifications of the IL-2 protein to increase or decrease its binding affinity for different components of the IL-2R[166]. The LILACS (Low-Dose Interleukin-2 in Patients with Stable Ischemic Heart Disease and Acute Coronary Syndrome) is a phase 1/2a clinical trial that is randomized, placebo-controlled, dose-escalation, and double-blind. This trial aims to increase the Treg subset in patients with acute coronary syndrome and evaluate its effects on clinical outcomes[167].

In conclusion, emerging T cell-based immunotherapies offer a promising route to prevent and possibly delay age-related diseases by addressing underlying immune mechanisms rather than only the affected tissues. Strategies to slow T cell senescence, deplete pathogenic lymphocytes, or boost immunoregulatory subsets hold significant potential for mitigating chronic inflammation. Further refining these approaches could pave the way for developing personalized treatments that exploit the beneficial immunomodulatory roles of T cells.

CONCLUDING REMARKS

This review has highlighted the state of the immune system during aging, focusing on both age-related changes and the cumulative impact of poor lifestyle habits that directly affect the function of the immune and cardiovascular systems. These changes particularly alter T cell function, disrupting the balance between Tregs and Th17 lymphocytes. This imbalance leads to chronic inflammation, loss of self-tolerance, and an increased risk of autoimmune diseases such as RA and SLE, as well as a heightened risk of CVDs, including atherosclerosis and AMI. Indeed, age-associated autoimmune disorders significantly contribute to the increased prevalence of CVDs in the elderly.

Overall, the overactivation of T cells and Tregs dysfunction are central to the pathogenesis of both autoimmune conditions and CVDs in aged patients, positioning aged T cells as potential therapeutic targets. However, the mechanisms by which aged T cells contribute to these diseases remain incompletely understood, with current studies offering limited descriptions of the complex interactions involved. Notably, there are very few registries examining different T cell populations and their correlation with the development of various ARDs, complicating efforts to establish causation and address these conditions effectively. Furthermore, the extent to which aging inherently changes our immune system, as opposed to changes driven by poor lifestyle habits, remains to be elucidated and is critical for the prevention of both CVDs and autoimmune disorders.

In conclusion, further research is needed to deepen our understanding of T cell dysregulation during aging, which is essential for developing treatments aimed at restoring the Treg/Th17 balance and alleviating the symptoms of age-related diseases.

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Authors' contributions

Conceived and supervised the study: Martín P
Conducted the literature search and wrote the manuscript: Ortega-Sollero E, Ruíz-Fernández I
All authors read and approved the final version of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethics approval and consent to participate

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REFERENCES

1. Wang J, Zhao X, Wan YY. Intricacies of TGF-β signaling in Treg and Th17 cell biology. *Cell Mol Immunol*. 2023;20:1002-22. DOI PubMed PMC
2. Knochelmann HM, Dwyer CJ, Bailey SR, et al. When worlds collide: Th17 and Treg cells in cancer and autoimmunity. *Cell Mol Immunol*. 2018;15:458-69. DOI PubMed PMC
3. Schmitt V, Rink L, Uciechowski P. The Th17/Treg balance is disturbed during aging. *Exp Gerontol*. 2013;48:1379-86. DOI PubMed
4. Ding T, Li B, Su R, et al. Elevated Th17 cells are associated with cardiovascular complications in ankylosing spondylitis. *Rheumatology*. 2022;61:3481-90. DOI
5. He X, Liang B, Gu N. Th17/Treg Imbalance and Atherosclerosis. *Dis Markers*. 2020;2020:8821029. DOI PubMed PMC
6. Mittelbrunn M, Kroemer G. Hallmarks of T cell aging. *Nat Immunol*. 2021;22:687-98. DOI PubMed
7. Wang Y, Dong C, Han Y, Gu Z, Sun C. Immunosenescence, aging and successful aging. *Front Immunol*. 2022;13:942796. DOI

PubMed PMC
8. Shirakawa K, Sano M. T cell immunosenescence in aging, obesity, and cardiovascular disease. *Cells.* 2021;10:2435. DOI PubMed PMC
9. Carrasco E, Gómez de Las Heras MM, Gabandé-Rodríguez E, Desdín-Micó G, Aranda JF, Mittelbrunn M. The role of T cells in age-related diseases. *Nat Rev Immunol.* 2022;22:97-111. DOI
10. Lee GR. The balance of Th17 versus treg cells in autoimmunity. *Int J Mol Sci.* 2018;19:730. DOI PubMed PMC
11. Zheng Y, Liu Q, Goronzy JJ, Weyand CM. Immune aging - A mechanism in autoimmune disease. *Semin Immunol.* 2023;69:101814. DOI PubMed PMC
12. Costantini E, D'Angelo C, Reale M. The Role of immunosenescence in neurodegenerative diseases. *Mediators Inflamm.* 2018;2018:6039171. DOI PubMed PMC
13. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circ Res.* 2018;123:825-48. DOI PubMed PMC
14. Heslinga M, Nielen MMJ, Smulders Y, Simsek S, Nurmohamed MT. Amplified prevalence and incidence of cardiovascular disease in patients with inflammatory arthritis and coexistent autoimmune disorders. *Rheumatology.* 2020;59:2448-54. DOI PubMed
15. Schwartz DM, Burma AM, Kitakule MM, Luo Y, Mehta NN. T cells in autoimmunity-associated cardiovascular diseases. *Front Immunol.* 2020;11:588776. DOI PubMed PMC
16. McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. *Immunity.* 2008;28:445-53. DOI
17. Rutz S, Eidenschenk C, Kiefer JR, Ouyang W. Post-translational regulation of RORγt-A therapeutic target for the modulation of interleukin-17-mediated responses in autoimmune diseases. *Cytokine Growth Factor Rev.* 2016;30:1-17. DOI PubMed
18. Yasuda K, Takeuchi Y, Hirota K. The pathogenicity of Th17 cells in autoimmune diseases. *Semin Immunopathol.* 2019;41:283-97. DOI
19. Keir ME, Yi T, Lu TT, Ghilardi N. The role of IL-22 in intestinal health and disease. *J Exp Med.* 2020;217:e20192195. DOI PubMed PMC
20. Veldhoen M. Interleukin 17 is a chief orchestrator of immunity. *Nat Immunol.* 2017;18:612-21. DOI PubMed
21. Taniki N, Nakamoto N, Chu PS, Ichikawa M, Teratani T, Kanai T. Th17 cells in the liver: balancing autoimmunity and pathogen defense. *Semin Immunopathol.* 2022;44:509-26. DOI PubMed
22. Pan Y, Yang W, Tang B, et al. The protective and pathogenic role of Th17 cell plasticity and function in the tumor microenvironment. *Front Immunol.* 2023;14:1192303. DOI PubMed PMC
23. Brucklacher-Waldert V, Ferreira C, Innocentin S, et al. Tbet or Continued RORγt expression is not required for Th17-associated immunopathology. *J Immunol.* 2016;196:4893-904. DOI
24. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet.* 2021;397:754-66. DOI PubMed
25. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science.* 2003;299:1057-61. DOI PubMed
26. Shevach EM, Thornton AM. tTregs, pTregs, and iTregs: similarities and differences. *Immunol Rev.* 2014;259:88-102. DOI PubMed PMC
27. Savage PA, Klawon DEJ, Miller CH. Regulatory T cell development. *Annu Rev Immunol.* 2020;38:421-53. DOI PubMed
28. Bilate AM, Lafaille JJ. Induced $CD4^+Foxp3^+$ regulatory T cells in immune tolerance. *Annu Rev Immunol.* 2012;30:733-58. DOI PubMed
29. Kanamori M, Nakatsukasa H, Okada M, Lu Q, Yoshimura A. Induced regulatory T cells: their development, stability, and applications. *Trends Immunol.* 2016;37:803-11. DOI
30. Miragaia RJ, Gomes T, Chomka A, et al. Single-cell transcriptomics of regulatory T cells reveals trajectories of tissue adaptation. *Immunity.* 2019;50:493-504.e7. DOI PubMed PMC
31. Goswami TK, Singh M, Dhawan M, et al. Regulatory T cells (Tregs) and their therapeutic potential against autoimmune disorders - Advances and challenges. *Hum Vaccin Immunother.* 2022;18:2035117. DOI PubMed PMC
32. Bauché D, Joyce-Shaikh B, Jain R, et al. $LAG3^+$ regulatory T cells restrain interleukin-23-producing $CX3CR1^+$ gut-resident macrophages during group 3 innate lymphoid cell-driven colitis. *Immunity.* 2018;49:342-52.e5. DOI
33. Tekguc M, Wing JB, Osaki M, Long J, Sakaguchi S. Treg-expressed CTLA-4 depletes CD80/CD86 by trogocytosis, releasing free PD-L1 on antigen-presenting cells. *Proc Natl Acad Sci USA.* 2021;118:e2023739118. DOI PubMed PMC
34. Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res.* 2012;72:917-27. DOI PubMed PMC
35. Okazaki T, Okazaki IM, Wang J, et al. PD-1 and LAG-3 inhibitory co-receptors act synergistically to prevent autoimmunity in mice. *J Exp Med.* 2011;208:395-407. DOI PubMed PMC
36. Ortiz MA, Diaz-Torné C, De Agustin JJ, et al. Altered CD39 and CD73 expression in rheumatoid arthritis: implications for disease activity and treatment response. *Biomolecules.* 2023;14:1. DOI PubMed PMC
37. Sojka DK, Huang YH, Fowell DJ. Mechanisms of regulatory T-cell suppression - a diverse arsenal for a moving target. *Immunology.* 2008;124:13-22. DOI PubMed PMC
38. Herrnstadt GR, Steinmetz OM. The role of Treg subtypes in glomerulonephritis. *Cell Tissue Res.* 2021;385:293-304. DOI PubMed PMC

39. Göschl L, Scheinecker C, Bonelli M. Treg cells in autoimmunity: from identification to Treg-based therapies. *Semin Immunopathol.* 2019;41:301-14. DOI PubMed
40. Shouse AN, LaPorte KM, Malek TR. Interleukin-2 signaling in the regulation of T cell biology in autoimmunity and cancer. *Immunity.* 2024;57:414-28. DOI PubMed PMC
41. Vignoli M, Ciullini Mannurita S, Fioravanti A, et al. CD25 deficiency: a new conformational mutation prevents the receptor expression on cell surface. *Clin Immunol.* 2019;201:15-9. DOI
42. Eggenhuizen PJ, Ng BH, Ooi JD. Treg enhancing therapies to treat autoimmune diseases. *Int J Mol Sci.* 2020;21:7015. DOI PubMed PMC
43. De Simone V, Franzè E, Ronchetti G, et al. Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. *Oncogene.* 2015;34:3493-503. DOI PubMed PMC
44. Qin Z, Wang R, Hou P, et al. TCR signaling induces STAT3 phosphorylation to promote TH17 cell differentiation. *J Exp Med.* 2024;221:e20230683. DOI PubMed PMC
45. Gorabi AM, Hajighasemi S, Kiaie N, et al. The pivotal role of CD69 in autoimmunity. *J Autoimmun.* 2020;111:102453. DOI
46. Cibrián D, Sánchez-Madrid F. CD69: from activation marker to metabolic gatekeeper. *Eur J Immunol.* 2017;47:946-53. DOI PubMed PMC
47. Jiménez-Fernández M, de la Fuente H, Martín P, Cibrián D, Sánchez-Madrid F. Unraveling Cd69 signaling pathways, ligands and laterally associated molecules. *EXCLI J.* 2023;22:334-51. DOI PubMed PMC
48. Kleinewietfeld M, Hafler DA. The plasticity of human Treg and Th17 cells and its role in autoimmunity. *Semin Immunol.* 2013;25:305-12. DOI PubMed PMC
49. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013;153:1194-217. DOI PubMed PMC
50. Schmauck-Medina T, Molière A, Lautrup S, et al. New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary. *Aging.* 2022;14:6829-39. DOI PubMed PMC
51. Li Z, Zhang Z, Ren Y, et al. Aging and age-related diseases: from mechanisms to therapeutic strategies. *Biogerontology.* 2021;22:165-87. DOI PubMed PMC
52. Liu Z, Liang Q, Ren Y, et al. Immunosenescence: molecular mechanisms and diseases. *Signal Transduct Target Ther.* 2023;8:200. DOI PubMed PMC
53. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-related diseases: role of inflammation triggers and cytokines. *Front Immunol.* 2018;9:586. DOI PubMed PMC
54. van den Akker EB, Makrodimitris S, Hulsman M, et al. Dynamic clonal hematopoiesis and functional T-cell immunity in a supercentenarian. *Leukemia.* 2021;35:2125-9. DOI PubMed PMC
55. Rodriguez IJ, Lalinde Ruiz N, Llano León M, et al. Immunosenescence study of T cells: a systematic review. *Front Immunol.* 2020;11:604591. DOI PubMed PMC
56. Han S, Georgiev P, Ringel AE, Sharpe AH, Haigis MC. Age-associated remodeling of T cell immunity and metabolism. *Cell Metab.* 2023;35:36-55. DOI PubMed PMC
57. Huang MC, Liao JJ, Bonasera S, Longo DL, Goetzl EJ. Nuclear factor-kappaB-dependent reversal of aging-induced alterations in T cell cytokines. *FASEB J.* 2008;22:2142-50. DOI
58. Lim MA, Lee J, Park JS, et al. Increased Th17 differentiation in aged mice is significantly associated with high IL-1β level and low IL-2 expression. *Exp Gerontol.* 2014;49:55-62. DOI
59. Churov AV, Mamashov KY, Novitskaia AV. Homeostasis and the functional roles of $CD4^+$ Treg cells in aging. *Immunol Lett.* 2020;226:83-9. DOI PubMed
60. Tsaknaridis L, Spencer L, Culbertson N, et al. Functional assay for human CD4+CD25+ Treg cells reveals an age-dependent loss of suppressive activity. *J Neurosci Res.* 2003;74:296-308. DOI
61. Sun L, Hurez VJ, Thibodeaux SR, et al. Aged regulatory T cells protect from autoimmune inflammation despite reduced STAT3 activation and decreased constraint of IL-17 producing T cells. *Aging Cell.* 2012;11:509-19. DOI
62. Jagger A, Shimojima Y, Goronzy JJ, Weyand CM. Regulatory T cells and the immune aging process: a mini-review. *Gerontology.* 2014;60:130-7. DOI PubMed PMC
63. Asami T, Endo K, Matsui R, et al. Long-term caloric restriction ameliorates T cell immunosenescence in mice. *Mech Ageing Dev.* 2022;206:111710. DOI
64. Wu C, Yosef N, Thalhamer T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature.* 2013;496:513-7. DOI PubMed PMC
65. Zhang S, Gang X, Yang S, et al. The alterations in and the role of the Th17/Treg balance in metabolic diseases. *Front Immunol.* 2021;12:678355. DOI PubMed PMC
66. Vriens A, Nawrot TS, Janssen BG, et al. Exposure to environmental pollutants and their association with biomarkers of aging: a multipollutant approach. *Environ Sci Technol.* 2019;53:5966-76. DOI
67. Ural BB, Caron DP, Dogra P, et al. Inhaled particulate accumulation with age impairs immune function and architecture in human lung lymph nodes. *Nat Med.* 2022;28:2622-32. DOI PubMed PMC
68. Qiu F, Liang CL, Liu H, et al. Impacts of cigarette smoking on immune responsiveness: up and down or upside down? *Oncotarget.* 2017;8:268-84. DOI PubMed PMC

69. Rocamora-Reverte L, Melzer FL, Würzner R, Weinberger B. The complex role of regulatory T cells in immunity and aging. *Front Immunol.* 2020;11:616949. DOI PubMed PMC
70. Lancaster JN, Keatinge-Clay DE, Srinivasan J, et al. Central tolerance is impaired in the middle-aged thymic environment. *Aging Cell.* 2022;21:e13624. DOI PubMed PMC
71. Youm YH, Kanneganti TD, Vandanmagsar B, et al. The Nlrp3 inflammasome promotes age-related thymic demise and immunosenescence. *Cell Rep.* 2012;1:56-68. DOI PubMed PMC
72. Chen R, Wang K, Feng Z, et al. CD147 deficiency in T cells prevents thymic involution by inhibiting the EMT process in TECs in the presence of TGFβ. *Cell Mol Immunol.* 2021;18:171-81. DOI PubMed PMC
73. Liang Z, Dong X, Zhang Z, Zhang Q, Zhao Y. Age-related thymic involution: Mechanisms and functional impact. *Aging Cell.* 2022;21:e13671. DOI PubMed PMC
74. Hemmers S, Schizas M, Azizi E, et al. IL-2 production by self-reactive CD4 thymocytes scales regulatory T cell generation in the thymus. *J Exp Med.* 2019;216:2466-78. DOI PubMed PMC
75. ElTanbouly MA, Noelle RJ. Rethinking peripheral T cell tolerance: checkpoints across a T cell's journey. *Nat Rev Immunol.* 2021;21:257-67. DOI
76. ElTanbouly MA, Zhao Y, Nowak E, et al. VISTA is a checkpoint regulator for naïve T cell quiescence and peripheral tolerance. *Science.* 2020;367:aay0524. DOI
77. Wang L, Le Mercier I, Putra J, et al. Disruption of the immune-checkpoint VISTA gene imparts a proinflammatory phenotype with predisposition to the development of autoimmunity. *Proc Natl Acad Sci USA.* 2014;111:14846-51. DOI PubMed PMC
78. Wong WF, Kohu K, Nakamura A, et al. Runx1 deficiency in CD4+ T cells causes fatal autoimmune inflammatory lung disease due to spontaneous hyperactivation of cells. *J Immunol.* 2012;188:5408-20. DOI
79. Oakley R, Tharakan B. Vascular hyperpermeability and aging. *Aging Dis.* 2014;5:114-25. DOI PubMed PMC
80. Erickson MA, Banks WA. Age-associated changes in the immune system and blood-brain barrier functions. *Int J Mol Sci.* 2019;20:1632. DOI PubMed PMC
81. McKinney EF, Lee JC, Jayne DR, Lyons PA, Smith KG. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. *Nature.* 2015;523:612-6. DOI PubMed PMC
82. Mogilenko DA, Shpynov O, Andhey PS, et al. Comprehensive profiling of an aging immune system reveals clonal GZMK$^+$ CD8$^+$ T cells as conserved hallmark of inflammaging. *Immunity.* 2021;54:99-115.e12. DOI
83. Kalekar LA, Schmiel SE, Nandiwada SL, et al. CD4$^+$ T cell anergy prevents autoimmunity and generates regulatory T cell precursors. *Nat Immunol.* 2016;17:304-14. DOI PubMed PMC
84. Maue AC, Yager EJ, Swain SL, Woodland DL, Blackman MA, Haynes L. T-cell immunosenescence: lessons learned from mouse models of aging. *Trends Immunol.* 2009;30:301-5. DOI PubMed PMC
85. Krüger P, Schroll M, Fenzl F, et al. Inflammation and fibrosis in progeria: organ-specific responses in an HGPS mouse model. *Int J Mol Sci.* 2024;25:9323. DOI PubMed PMC
86. Zaghini A, Sarli G, Barboni C, et al. Long term breeding of the Lmna G609G progeric mouse: characterization of homozygous and heterozygous models. *Exp Gerontol.* 2020;130:110784. DOI
87. Bravo-Ferrer I, Cuartero MI, Medina V, et al. Lack of the aryl hydrocarbon receptor accelerates aging in mice. *FASEB J.* 2019;33:12644-54. DOI
88. Desdín-Micó G, Soto-Heredero G, Aranda JF, et al. T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. *Science.* 2020;368:1371-6. DOI PubMed PMC
89. Brinks R, Hoyer A, Weber S, et al. Age-specific and sex-specific incidence of systemic lupus erythematosus: an estimate from cross-sectional claims data of 2.3 million people in the German statutory health insurance 2002. *Lupus Sci Med.* 2016;3:e000181. DOI PubMed PMC
90. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med.* 2020;172:ITC81-96. DOI PubMed
91. Shan J, Jin H, Xu Y. T Cell metabolism: a new perspective on Th17/Treg cell imbalance in systemic lupus erythematosus. *Front Immunol.* 2020;11:1027. DOI PubMed PMC
92. Yusoff F, Wong KK, Mohd Redzwan N. Th1, Th2, and Th17 cytokines in systemic lupus erythematosus. *Autoimmunity.* 2020;53:8-20. DOI PubMed
93. Li H, Boulougoura A, Endo Y, Tsokos GC. Abnormalities of T cells in systemic lupus erythematosus: new insights in pathogenesis and therapeutic strategies. *J Autoimmun.* 2022;132:102870. DOI PubMed
94. Li Y, Wang R, Liu S, et al. Interleukin-25 is upregulated in patients with systemic lupus erythematosus and ameliorates murine lupus by inhibiting inflammatory cytokine production. *Int Immunopharmacol.* 2019;74:105680. DOI
95. Sharabi A, Tsokos GC. T cell metabolism: new insights in systemic lupus erythematosus pathogenesis and therapy. *Nat Rev Rheumatol.* 2020;16:100-12. DOI PubMed
96. Wang R, Dillon CP, Shi LZ, et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity.* 2011;35:871-82. DOI PubMed PMC
97. Delgoffe GM, Kole TP, Zheng Y, et al. The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. *Immunity.* 2009;30:832-44. DOI PubMed PMC
98. Niu Q, Cai B, Huang ZC, Shi YY, Wang LL. Disturbed Th17/Treg balance in patients with rheumatoid arthritis. *Rheumatol Int.* 2012;32:2731-6. DOI PubMed

99. Li Y, Shen Y, Hohensinner P, et al. Deficient activity of the nuclease MRE11A induces T cell aging and promotes arthritogenic effector functions in patients with rheumatoid arthritis. *Immunity*. 2016;45:903-16. DOI PubMed PMC
100. Paradowska-Gorycka A, Wajda A, Romanowska-Próchnicka K, et al. Th17/Treg-related transcriptional factor expression and cytokine profile in patients with rheumatoid arthritis. *Front Immunol.* 2020;11:572858. DOI PubMed PMC
101. Pesce B, Soto L, Sabugo F, et al. Effect of interleukin-6 receptor blockade on the balance between regulatory T cells and T helper type 17 cells in rheumatoid arthritis patients. *Clin Exp Immunol.* 2013;171:237-42. DOI PubMed PMC
102. Komiyama Y, Nakae S, Matsuki T, et al. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *J Immunol.* 2006;177:566-73. DOI
103. Habbestad A, Willumsen JS, Aarseth JH, et al. Increasing age of multiple sclerosis onset from 1920 to 2022: a population-based study. *J Neurol.* 2024;271:1610-7. DOI PubMed PMC
104. Ruiz-Fernández I, Sánchez-Díaz R, Ortega-Sollero E, Martín P. Update on the role of T cells in cognitive impairment. *Br J Pharmacol.* 2024;181:799-815. DOI PubMed
105. Bolton C, Smith PA. The influence and impact of ageing and immunosenescence (ISC) on adaptive immunity during multiple sclerosis (MS) and the animal counterpart experimental autoimmune encephalomyelitis (EAE). *Ageing Res Rev.* 2018;41:64-81. DOI PubMed
106. Capasso N, Virgilio E, Covelli A, et al. Aging in multiple sclerosis: from childhood to old age, etiopathogenesis, and unmet needs: a narrative review. *Front Neurol.* 2023;14:1207617. DOI PubMed PMC
107. Moser T, Akgün K, Proschmann U, Sellner J, Ziemssen T. The role of TH17 cells in multiple sclerosis: therapeutic implications. *Autoimmun Rev.* 2020;19:102647. DOI PubMed
108. Liu R, Du S, Zhao L, et al. Autoreactive lymphocytes in multiple sclerosis: pathogenesis and treatment target. *Front Immunol.* 2022;13:996469. DOI PubMed PMC
109. Schwab N, Schneider-Hohendorf T, Wiendl H. Therapeutic uses of anti-α4-integrin (anti-VLA-4) antibodies in multiple sclerosis. *Int Immunol.* 2015;27:47-53. DOI PubMed
110. Starost L, Lindner M, Herold M, et al. Extrinsic immune cell-derived, but not intrinsic oligodendroglial factors contribute to oligodendroglial differentiation block in multiple sclerosis. *Acta Neuropathol.* 2020;140:715-36. DOI PubMed PMC
111. Palle P, Monaghan KL, Milne SM, Wan ECK. Cytokine signaling in multiple sclerosis and its therapeutic applications. *Med Sci.* 2017;5:23. DOI PubMed PMC
112. Bai Z, Chen D, Wang L, et al. Cerebrospinal fluid and blood cytokines as biomarkers for multiple sclerosis: a systematic review and meta-analysis of 226 studies with 13,526 multiple sclerosis patients. *Front Neurosci.* 2019;13:1026. DOI PubMed PMC
113. Mexhitaj I, Nyirenda MH, Li R, et al. Abnormal effector and regulatory T cell subsets in paediatric-onset multiple sclerosis. *Brain.* 2019;142:617-32. DOI PubMed PMC
114. Kaskow BJ, Baecher-Allan C. Effector T Cells in multiple sclerosis. *Cold Spring Harb Perspect Med.* 2018;8:a029025. DOI PubMed PMC
115. Kundu S, Freiberg MS, Tracy RP, et al. Circulating T cells and cardiovascular risk in people with and without HIV infection. *J Am Coll Cardiol.* 2022;80:1633-44. DOI PubMed PMC
116. Sun Z. Aging, arterial stiffness, and hypertension. *Hypertension.* 2015;65:252-6. DOI
117. Ren J, Crowley SD. Role of T-cell activation in salt-sensitive hypertension. *Am J Physiol Heart Circ Physiol.* 2019;316:H1345-53. DOI PubMed PMC
118. Yu HT, Park S, Shin EC, Lee WW. T cell senescence and cardiovascular diseases. *Clin Exp Med.* 2016;16:257-63. DOI
119. Pan XX, Wu F, Chen XH, et al. T-cell senescence accelerates angiotensin II-induced target organ damage. *Cardiovasc Res.* 2021;117:271-83. DOI
120. Higaki A. The chicken or the egg: the role of T cell polarity in salt-sensitive hypertension. *Hypertens Res.* 2023;46:2425-7. DOI PubMed
121. Barhoumi T, Kasal DA, Li MW, et al. T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. *Hypertension.* 2011;57:469-76. DOI
122. Watanabe R, Hosgur E, Zhang H, et al. Pro-inflammatory and anti-inflammatory T cells in giant cell arteritis. *Joint Bone Spine.* 2017;84:421-6. DOI PubMed PMC
123. Espígol-Frigolé G, Corbera-Bellalta M, Planas-Rigol E, et al. Increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with giant-cell arteritis. *Ann Rheum Dis.* 2013;72:1481-7. DOI
124. Wen Z, Shimojima Y, Shirai T, et al. NADPH oxidase deficiency underlies dysfunction of aged CD8+ Tregs. *J Clin Invest.* 2016;126:1953-67. DOI PubMed PMC
125. Nakagawa H, Wang L, Cantor H, Kim HJ. Chapter One - New Insights into the biology of CD8 regulatory T cells. *Adv Immunol.* 2018;140:1-20. DOI PubMed
126. Saigusa R, Winkels H, Ley K. T cell subsets and functions in atherosclerosis. *Nat Rev Cardiol.* 2020;17:387-401. DOI PubMed PMC
127. Cheng X, Yu X, Ding YJ, et al. The Th17/Treg imbalance in patients with acute coronary syndrome. *Clin Immunol.* 2008;127:89-97. DOI
128. Sánchez-Díaz R, Blanco-Dominguez R, Lasarte S, et al. Thymus-derived regulatory T cell development is regulated by C-type lectin-mediated BIC/MicroRNA 155 expression. *Mol Cell Biol.* 2017;37:e00341-16. DOI PubMed PMC

129. Tsilingiri K, de la Fuente H, Relaño M, et al. Oxidized low-density lipoprotein receptor in lymphocytes prevents atherosclerosis and predicts subclinical disease. *Circulation.* 2019;139:243-55. DOI PubMed
130. Erbel C, Chen L, Bea F, et al. Inhibition of IL-17A attenuates atherosclerotic lesion development in apoE-deficient mice. *J Immunol.* 2009;183:8167-75. DOI
131. Danzaki K, Matsui Y, Ikesue M, et al. Interleukin-17A deficiency accelerates unstable atherosclerotic plaque formation in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol.* 2012;32:273-80. DOI
132. Suda M, Paul KH, Minamino T, et al. Senescent cells: a therapeutic target in cardiovascular diseases. *Cells.* 2023;12:1296. DOI PubMed PMC
133. Haghikia A, Zimmermann F, Schumann P, et al. Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism. *Eur Heart J.* 2022;43:518-33. DOI PubMed PMC
134. Saleh M, Ambrose JA. Understanding myocardial infarction. *F1000Res.* 2018;7:1378. DOI PubMed PMC
135. Liu J, Liu F, Liang T, et al. The roles of Th cells in myocardial infarction. *Cell Death Discov.* 2024;10:287. DOI PubMed PMC
136. Kino T, Khan M, Mohsin S. The regulatory role of T cell responses in cardiac remodeling following myocardial infarction. *Int J Mol Sci.* 2020;21:5013. DOI PubMed PMC
137. Kubota A, Suto A, Suga K, et al. Inhibition of Interleukin-21 prolongs the survival through the promotion of wound healing after myocardial infarction. *J Mol Cell Cardiol.* 2021;159:48-61. DOI
138. Youn JC, Jung MK, Yu HT, et al. Increased frequency of $CD4^{+}CD57^{+}$ senescent T cells in patients with newly diagnosed acute heart failure: exploring new pathogenic mechanisms with clinical relevance. *Sci Rep.* 2019;9:12887. DOI PubMed PMC
139. Delgobo M, Weiß E, Ashour D, et al. Myocardial milieu favors local differentiation of regulatory T cells. *Circ Res.* 2023;132:565-82. DOI PubMed
140. Blanco-Domínguez R, de la Fuente H, Rodríguez C, et al. CD69 expression on regulatory T cells protects from immune damage after myocardial infarction. *J Clin Invest.* 2022;132:e52418. DOI
141. Lampejo T, Durkin SM, Bhatt N, Guttmann O. Acute myocarditis: aetiology, diagnosis and management. *Clin Med.* 2021;21:e505-10. DOI PubMed PMC
142. Munir AZ, Gutierrez A, Qin J, Lichtman AH, Moslehi JJ. Immune-checkpoint inhibitor-mediated myocarditis: CTLA4, PD1 and LAG3 in the heart. *Nat Rev Cancer.* 2024;24:540-53. DOI PubMed
143. Fenioux C, Abbar B, Boussouar S, et al. Thymus alterations and susceptibility to immune checkpoint inhibitor myocarditis. *Nat Med.* 2023;29:3100-10. DOI
144. Jiménez-Alejandre R, Ruiz-Fernández I, Martín P. Pathophysiology of immune checkpoint inhibitor-induced myocarditis. *Cancers.* 2022;14:4494. DOI PubMed PMC
145. Blanco-Domínguez R, Sánchez-Díaz R, de la Fuente H, et al. A novel circulating MicroRNA for the detection of acute myocarditis. *N Engl J Med.* 2021;384:2014-27. DOI PubMed PMC
146. Cruz-Adalia A, Jiménez-Borreguero LJ, Ramírez-Huesca M, et al. CD69 limits the severity of cardiomyopathy after autoimmune myocarditis. *Circulation.* 2010;122:1396-404. DOI
147. Ramos GC, van den Berg A, Nunes-Silva V, et al. Myocardial aging as a T-cell-mediated phenomenon. *Proc Natl Acad Sci USA.* 2017;114:E2420-9. DOI PubMed PMC
148. Ammirati E, Frigerio M, Adler ED, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail.* 2020;13:e007405. DOI PubMed PMC
149. Porsch F, Binder CJ. Autoimmune diseases and atherosclerotic cardiovascular disease. *Nat Rev Cardiol.* 2024;21:780-807. DOI PubMed
150. Pan SY, Tian HM, Zhu Y, et al. Cardiac damage in autoimmune diseases: Target organ involvement that cannot be ignored. *Front Immunol.* 2022;13:1056400. DOI PubMed PMC
151. Martini E, Cremonesi M, Felicetta A, et al. Autoimmune-like mechanism in heart failure enables preventive vaccine therapy. *Circ Res.* 2025;136:4-25. DOI PubMed PMC
152. Robinson G, Pineda-Torra I, Ciurtin C, Jury EC. Lipid metabolism in autoimmune rheumatic disease: implications for modern and conventional therapies. *J Clin Invest.* 2022;132:e148552. DOI PubMed PMC
153. Purmalek MM, Carlucci PM, Dey AK, et al. Association of lipoprotein subfractions and glycoprotein acetylation with coronary plaque burden in SLE. *Lupus Sci Med.* 2019;6:e000332. DOI PubMed PMC
154. Baardman J, Lutgens E. Regulatory T cell metabolism in atherosclerosis. *Metabolites.* 2020;10:279. DOI PubMed PMC
155. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol.* 2003;23:168-75. DOI PubMed
156. Alghareeb R, Hussain A, Maheshwari MV, Khalid N, Patel PD. Cardiovascular complications in systemic lupus erythematosus. *Cureus.* 2022;14:e26671. DOI PubMed PMC
157. Kessler J, Totoson P, Devaux S, Moretto J, Wendling D, Demougeot C. Animal models to study pathogenesis and treatments of cardiac disorders in rheumatoid arthritis: Advances and challenges for clinical translation. *Pharmacol Res.* 2021;170:105494. DOI PubMed
158. Dai H, Wang X, Yin S, et al. Atrial fibrillation promotion in a rat model of rheumatoid arthritis. *J Am Heart Assoc.* 2017;6:007320. DOI PubMed PMC
159. Wang X, Fan H, Wang Y, et al. Elevated peripheral T helper cells are associated with atrial fibrillation in patients with rheumatoid

arthritis. *Front Immunol.* 2021;12:744254. DOI PubMed PMC

160. Amor C, Feucht J, Leibold J, et al. Senolytic CAR T cells reverse senescence-associated pathologies. *Nature.* 2020;583:127-32. DOI PubMed PMC
161. Deng Y, Kumar A, Xie K, et al. Targeting senescent cells with NKG2D-CAR T cells. *Cell Death Discov.* 2024;10:217. DOI PubMed PMC
162. Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. *Nat Rev Nephrol.* 2022;18:611-27. DOI PubMed PMC
163. Notley CA, McCann FE, Inglis JJ, Williams RO. ANTI-CD3 therapy expands the numbers of CD4+ and CD8+ Treg cells and induces sustained amelioration of collagen-induced arthritis. *Arthritis Rheum.* 2010;62:171-8. DOI PubMed
164. Bryl E, Vallejo AN, Matteson EL, Witkowski JM, Weyand CM, Goronzy JJ. Modulation of CD28 expression with anti-tumor necrosis factor alpha therapy in rheumatoid arthritis. *Arthritis Rheum.* 2005;52:2996-3003. DOI PubMed
165. Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) immunotherapy. *Cold Spring Harb Perspect Biol.* 2018;10:a028456. DOI PubMed PMC
166. Zhao TX, Newland SA, Mallat Z. 2019 ATVB plenary lecture: interleukin-2 therapy in cardiovascular disease: the potential to regulate innate and adaptive immunity. *Arterioscler Thromb Vasc Biol.* 2020;40:853-64. DOI PubMed
167. Zhao TX, Kostapanos M, Griffiths C, et al. Low-dose interleukin-2 in patients with stable ischaemic heart disease and acute coronary syndromes (LILACS): protocol and study rationale for a randomised, double-blind, placebo-controlled, phase I/II clinical trial. *BMJ Open.* 2018;8:e022452. DOI PubMed PMC